REMARKS

Claim 73 has been cancelled without prejudice.

In claim 70 and 72, the phrase "or a carbohydrate" has been deleted and the word "or" has been inserted after the word "glycoprotein".

Applicant believes that none of the amendments above add new matter to the specification.

PATENTABILITY ARGUMENTS

A. Rejections under 35 U.S.C. §112 First Paragraph

The Examiner has rejected claims 69-72 under 35 USC §112, first paragraph, as failing to comply with the written description requirement. More specifically the Examiner states that the subject matter is not adequately described in the specification in such a way as to convey that the inventor's had possession of the claimed invention at the time the application was filed. He further states that it is not readily clear where in the specification biomolecule/polymer conjugates as claimed are disclosed. Applicant respectfully disagrees.

The specification defines a polynucleotide on page 8, lines 30-31 as "DNA or RNA >50 bases...", oligonucleotide on page 9, lines 1-3 as DNA, RNA ... sequences <100 bases...", RNA on page 10, lines 8-13 as "ribonucleic acid ... of any length", DNA on page 10, lines 8-13 as "deoxyribonucleic acid... of any length". These definitions are a class of biomolecules, *i.e.* nucleic acids, which have been given different designations in the industry based solely on the length of the particular molecule of interest. Because they are a class they react similarly in chemical reactions and with generally expected results. Such as for example in 5' nucleic acid modification reactions or in incorporation of modified bases during nucleic acid synthesis reactions. In cases where this might not be the case one skilled in the art would be able to modify the experimental protocol without undue experimentation and obtain desired results.

Proteins, glycoprotein and peptides are a class of biomolecules comprising amino acid building blocks that contain an amino terminus and often contain an amine group within their side chain. These amine groups are utilized by the present invention to incorporate hydrazine, oxyamino or aldehyde groups onto the biomolecule. The amines in these biomolecules react similarly in chemical reactions and with generally expected results. Such as for example the modification of the amines with SHNH or SFB (*see* Figure 2, patent application serial no.: 09/815,978 incorporated by reference in its entirety) or SONH. In cases where this might not be the case one skilled in the art would be able to modify the experimental protocol without undue experimentation and obtain desired results.

In addition, the polymers, poly-L-lysine, poly-L-ornithine and polyethyleneimine are a class of polymers having amine groups that may be utilized by the present invention to incorporate hydrazine, oxyamino or aldehyde groups onto the polymer. The amines of these polymers react similarly in chemical reactions and with generally expected results. Such as for example the modification of the amines with SHNH or SFB (*see* Figure 2, patent application serial no.: 09/815,978 incorporated by reference in its entirety) or SONH. In cases where this might not be the case one skilled in the art would be able to modify the experimental protocol without undue experimentation and obtain desired results.

The Examiner is directed to the Examples of the specification, more specifically, Example 1 teaches the preparation of 5'-aldehyde modified oligonucleotides, hydrazine containing polyethyleneimine, hydrazine containing poly-L-lysine and the conjugation of the 5'-aldehyde modified oligonucleotide with hydrazine containing poly-L-lysine. One skilled in the art using the teaching of the preparation of HyNic:poly-L-lysine would be able to prepare HyNic:poly-L-ornithine without undue experimentation. In addition, one skilled in the art would be able to conjugate the 5'aldehyde modified oligonucleotide with the hydrazine containing polyethyleneimine or 5'aldehyde modified oligonucleotide with hydrazine containing poly-L-ornithine using the teaching of the preparation of oligonucleotide/HyNic:poly-L-lysine conjugate without undue experimentation.

Example 2 teaches the preparation of aldyhyde modified poly-L-lysine , 5'-hydrazine modified oligonucleotide and conjugation of hydrazine-modified oligonucleotide to aldehyde modified poly-L-lysine. One skilled in the art using the teaching of the preparation of aldehyde modified poly-L-lysine would be able to prepare aldehyde modified poly-L-ornithine or aldehyde modified polyethyleneimine without undue experimentation. In addition, one skilled in the art would be able to conjugate these aldehyde modified polymers with the hydrazine containing oligonucleotide using the teaching of conjugation of the hydrazine modified oligonucleotide to aldehyde modified poly-L-lysine without undue experimentation.

Example 6 teaches the preparation of aldehyde modified proteins and conjugation of aldehyde modified proteins to HyNic:poly-L-lysine. One skilled in the art using the teaching of the preparation of aldehyde modified proteins would be able to prepare aldehyde modified glycoproteins or peptides without undue experimentation (see page 29, lines 20-26 for oxidation with sodium periodate to cleave 1, 2-diol groups on carbohydrates to produce aldehydes. In addition, one skilled in the art would be able to conjugate these aldehyde modified proteins, glycoprotiens and peptides with the hydrazine containing polymers including poly-L-ornithine and polyethyleneimine using the teaching of conjugation of the aldehyde modified proteins to HyNic:poly-L-lysine without undue experimentation.

Example 7 teaches the preparation of hydrazine modified proteins. One skilled in the art using the teaching of the preparation of hydrazine modified proteins would be able to prepare hydrazine modified glycoproteins or peptides without undue experimentation. In addition, one skilled in the art would be able to conjugate these hydrazine modified

proteins, glycoprotiens and peptides with the aldehyde containing polymers poly-L-lysine, poly-L-ornithine and polyethyleneimine using the teaching of conjugation of the hydrazine-modified oligonucleotide to aldehyde-modified poly-L-lysine without undue experimentation.

Applicant has incorporated by reference patent application serial no.: 09/815,978 ("978") tilted "Hydrazine-based and carbonyl-based bifunctional crosslinking reagents" filed 22 March 2000 into this specification. Examples 24, 26 and 27 are directed to the preparation of aliphatic succinimidyl oxyamino hydrochloride , preparation of a bifunctional aromatic oxyammonium hydrochloride, -O-oxyammoniumnicotinate hydrochloride (SONH), and preparation of an oxyamino-modified protein, respectively. In addition, Figure 9 shows a synthetic scheme for the synthesis of an aminooxy crosslinking reagent (SONH). Further example 22 references a commercially available compound amino-C6-amidite used in the synthesis of nucleic acids to incorporate an amino group at the 5' terminus. The sucinimidyl group contained in SONH will react with the free amines available on poly-L-lysine, poly-L-ornithine and or polyethyleneimine to produce a polymer having an oxyamino group that in the presence of a aldehyde modified biomolecule will form a polymer/biomolecule conjugate joined via oxime bond. In addition, the sucinimidyl group contained in SONH will react with the free amines available on the 5' terminus of the modified nucleic acids or free amine groups available on proteins, glycoproteins or peptides to produce a biomolecule having an oxyamino group that in the presence of a aldehyde on a polymer will form a biomolecule/polymer conjugate joined via oxime bond. Clearly one skilled in the art using the teaching of examples 24, 26 and 27 of patent application 09/815,978 and the teaching of example 6 in this specification would be able to produce a conjugate of a biomolecule and polymer joined via an oxime bond without undue experimentation.

In view of the arguments presented above Applicant respectfully requests that the Examiner remove these rejections.

B. Rejections under 35 U.S.C §103(a)

Under 35 U.S.C. 103 (a) the Examiner must provide a motivation to combine the references sited, show that one skilled in the art would have a reasonable expectation of success in combining the teachings of the references and demonstrate that the references teach all the limitations of the rejected claim. The Examiner boldly states that it would have been obvious to couple a nucleic acid to poly-L-lysine as suggested by 436 in view of the binding of a nucleic acid to a solid support as suggested by 055 and using such a bond during nucleic acid synthesis as taught by 682. Applicant fails to see the motiviation or the reasonable expectation of success.

More specifically, patent 436 does not teach binding a nucleic acid to polylysine. Patent 436 merely suggests the binding of polylysine to a solid support to achieve a multiplicity of binding when attaching nucleic acids to the polylysine. Further patent 436 does not teach how one skilled in the art is to attach the nucleic acid(s) to the polylysine via a hydrazone bond but rather teaches the use of steptavidin/biotin couple pair to bind

nucleic acids to beads. Patent 055 suggests using a hydrazone bond when binding amplified target nucleic acids to a surface for the purpose of purification for later mass spectral analysis. This patent suggests that one could bind nucleic acids to a surface using a hydrazone bind but does not teach one skilled in the art how that would be accomplished. Rather this patent teaches use of steptavidin/biotin couple pair to bind nucleic acids to beads. Patent 682 teaches the preparation of an oligonucleotide having hydrazone internucleosidyl linkages for use in instituting structural characteristics to the oligonucleotide that mimic naturally occurring nucleic acids for therapeutic applications. However, once again this patent does not provide a teaching on how one skilled in the art would attach nucleic acids to a poly-L-lysine polymer but describes how one would synthesize a nucleic acid having hydrazone internucleosidyl linkages. Finally, patent 734 teaches the fluorescent labeling of a nucleic acid molecule via hydrazone bond. Unfortunately, this patent like the others cited does teach how one skilled in the art would attach a nucleic acid to a poly-L-lysine polymer. In fact, none of the references cited by the Examiner teach how one skilled in the art would be able to bind a nucleic acid molecule to a poly-L-lysine polymer via a hydrazone bond. Clearly the free amines contained on poly-L-lysine will not by themselves form the claimed hydrazone or oxime bonds with a nucleic acid molecule without modification. None of the references cited by the Examiner provide such as teaching to allow one skilled in the art to make and use Applicant's invention. Absent this, there would be no motivation to combine the references because by combining the cited references one skilled in the art would not be able to obtain Applicant's invention. Clearly, if one were to attempt to combine the references there would be no reasonable expectation of success because no teaching is provided to permit one skilled in the art to make Applicant's invention. Finally, absent a teaching of how one skilled in the art would bind a nucleic acid to a poly-L-lysine polymer the Examiner has not provided references in which all the limitations of claim 69 are taught.

Next the Examiner rejects claim 71 under 35 U.S.C §103(a) as being unpatentable over Koster *et al.* (6,133,436) "436" in view of Cook *et al.* (5,783,682) "682". The Examiner states that Applicant's claim is directed to a biomolecule/polymer conjugate wherein the biomolecule is conjugated to the polymer by a oxime bond, and the biomolecule is a polynucleotide, oligonucleotide, DNA or RNA and the polymer is poly-lysine, poly-L-ornithine or polyethyleneimine. He suggests that 436 discloses covalently attaching nucleic acids to beads attached to a solid support and that the linking group such as polylysine can be used to bind the beads to the support or nucleic acid to the beads and 682 discloses using an oxime linkages when carrying out nucleic acid synthesis on a solid support. The Examiner concludes that it would have been obvious to use an oxime bond to couple a nucleic acid to polylysine when using the polylysine to couple a nucleic acid to beads as disclosed by 436 as suggested by 682 using oxime linkages when carrying out nucleic acid synthesis on solid support. Applicant respectfully disagrees and fails to see the motiviation or the reasonable expectation of success.

As stated above patent 436 does not teach binding a nucleic acid to polylysine. Patent 436 merely suggests the binding of polylysine to a solid support to achieve a multiplicity of binding when attaching nucleic acids to the polylysine. Further patent 436 does not

teach how one skilled in the art is to attach the nucleic acid(s) to the polylysine via a hydrazone bond but rather teaches the use of steptavidin/biotin couple pair to bind nucleic acids to beads. Patent 055 suggests using a hydrazone bond when binding amplified target nucleic acids to a surface for the purpose of purification for later mass spectral analysis. This patent suggests that one could bind nucleic acids to a surface using a hydrazone bind but does not teach one skilled in the art how that would be accomplished. Rather this patent teaches use of steptavidin/biotin couple pair to bind nucleic acids to beads. Patent 307 teaches the preparation of an oligonucleotide having oxime internucleosidyl linkages for use in instituting structural characteristics to the oligonucleotide that exhibit chemical and/or enzymatic stability relative to their naturally occuring counterparts for therapeutic applications. However, once again this patent does not provide a teaching on how one skilled in the art would attach nucleic acids to a poly-L-lysine polymer but describes how one would synthesize a nucleic acid having oxime internucleosidyl linkages. Absent this, there would be no motivation to combine the references because by combining the cited references one skilled in the art would not be able to obtain Applicant's invention. Clearly, if one were to attempt to combine the references there would be no reasonable expectation of success because no teaching is provided to permit one skilled in the art to make Applicant's invention. Finally, absent a teaching of how one skilled in the art would bind a nucleic acid to a poly-L-lysine polymer the Examiner has not provided references in which all the limitations of claim 71 are taught.

The mere suggestion by the Examiner that the polylysine incidentally mentioned in 436 could have been substituted for the solid support in 055 for the binding of nucleic acids via a hydrazone bond, or for binding nucleic acids via an oxime bond as taught in 307 for joining nucleosides to form an oligonucleotide, without more does not constitute a description of Applicant's compound (MPEP 2121.02, In re Hoeksena 399 F2d. 269, 158 USPQ 596 (CCPA, 1968)). 35 U.S.C. 112 first paragraph states that a specification "shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same..." . Without such a description a claim is rejected as "failing to comply with the written description requirement..." because the "claim contains subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed had possession of the claimed invention." More specifically the written description in the specification does not teach one skilled in the art how to make and use the invention. Consequently, the inventor is deemed to not have had possession of the claimed invention. MPEP 2121.01 subsection II states that "even if a reference discloses an inoperable device it is prior art for all it teaches". Then if the reference does not provide a teaching or a description of how one skilled in the art would combine polylysine with nucleic acids via a hydrazone or an oxime bond then the reference cannot act as prior art. In principle the compound was not previously described. Because the references sited by the Examiner do not teach one skilled in the art how to combine poly-L-lysine with nucleic acids via a hydrazone bond nor an oxime bond the references are not prior art and Applicant respectfully requests that the Examiner remove these rejections.

Applicant respectfully requests that in view of these new claims the Examiner remove these rejections.

CONCLUSION

In view of above, the invention now satisfies the statutory requirements for patentability. Applicant respectfully requests that the Examiner issue an allowance of the claims.

Respectfully submitted,

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